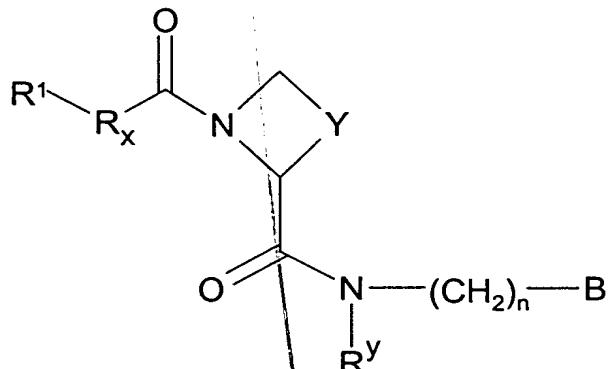


Claims

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1. A compound of formula I,



5

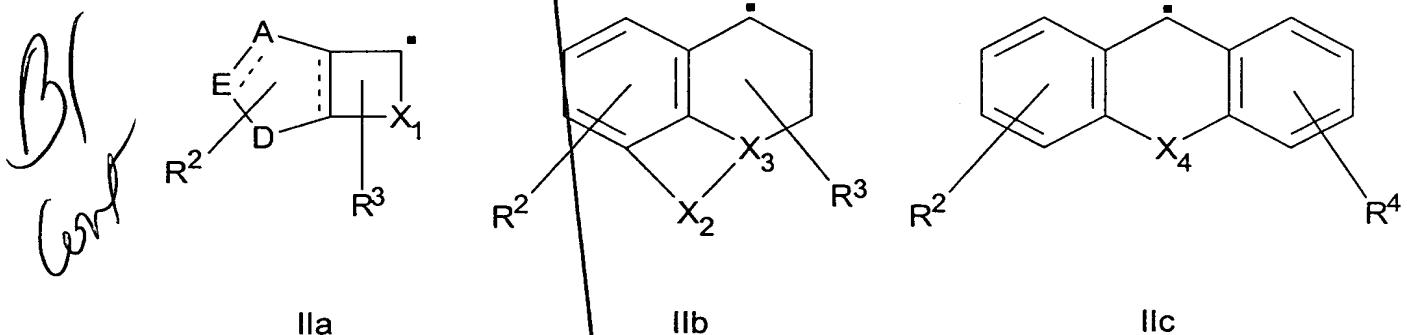
wherein

10 R^1 represents H, C_{1-4} alkyl (optionally substituted by one or more substituents selected from cyano, halo, OH, $C(O)OR^{1a}$ or $C(O)N(R^{1b})R^{1c}$) or OR^{1d} ;

15 R^{1d} represents H, $C(O)R^{11}$, $SiR^{12}R^{13}R^{14}$ or C_{1-6} alkyl, which latter group is optionally substituted or terminated by one or more substituent selected from OR^{15} or $(CH_2)_qR^{16}$;

20 R^{12} , R^{13} and R^{14} independently represent H, phenyl or C_{1-6} alkyl; R^{16} represents C_{1-4} alkyl, phenyl, OH, $C(O)OR^{17}$ or $C(O)N(H)R^{18}$; R^{18} represents H, C_{1-4} alkyl or $CH_2C(O)OR^{19}$; R^{15} and R^{17} independently represent H, C_{1-6} alkyl or C_{1-3} alkylphenyl; R^{1a} , R^{1b} , R^{1c} , R^{11} and R^{19} independently represent H or C_{1-4} alkyl; and q represents 0, 1 or 2;

R_x represents a structural fragment of formula IIa, IIb or IIc,



5 wherein

the dotted lines independently represent optional bonds;

A and E independently represent O or S, CH or CH₂ (as appropriate), or N or N(R²¹) (as appropriate);

D represents $-\text{CH}_2-$, O, S, $\text{N}(\text{R}^{22})$, $-(\text{CH}_2)_2-$, $-\text{CH}=\text{CH}-$, $-\text{CH}_2\text{N}(\text{R}^{22})-$,

-N(R²²)CH₂-, -CH=N-, -N=CH-, -CH₂O-, -OCH₂-, -CH₂S- or -SCH₂-;

X_1 represents C_{2-4} alkylene; C_{2-3} alkylene interrupted by Z ; $-C(O)-Z-A^1-$;

-Z-C(O)-A¹-; -CH₂-C(O)-A¹-; -Z-C(O)-Z-A²-; -CH₂-Z-C(O)-A²-;

-Z-CH₂-C(O)-A²⁻; -Z-CH₂-S(O)_m-A²⁻; -C(O)-A³⁻; -Z-A³⁻; or -A³⁻Z-;

X_2 represents C_{2-3} alkylene, $-C(O)-A^4-$ or $-A^4-C(O)-$;

X_3 represents CH or N;

X_4 represents a single bond, O, S, C(O), N(R²³), -CH(R²³)-,

-CH(R²³)-CH(R²⁴)- or -C(R²³)=C(R²⁴)-;

A^1 represents a single bond or C_{1-2} alkylene;

A^2 represents a single bond or $-\text{CH}_2-$;

A^3 represents C_{1-3} alkylene;

A^4 represents C(O) or C_{1-2} alkylene;

Z represents, at each occurrence, O, S(O)_m or N(R²⁵);

R^2 and R^4 independently represent one or more optional substituents

selected from C_{1-4} alkyl, C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo substituent), methylenedioxy, halo, hydroxy, cyano, nitro, $S(O)_2NH_2$, $C(O)OR^{26}$, SR^{26} , $S(O)R^{26a}$, $S(O)_2R^{26a}$ or $N(R^{27})R^{28}$;

5 R^3 represents one or more optional substituents selected from OH, C_{1-4} alkoxy, C_{1-6} alkyl (optionally substituted by one or more halo group), or $N(R^{29a})R^{29b}$;

R^{25} , R^{29a} and R^{29b} independently represent H, C_{1-4} alkyl or $C(O)R^{30}$;

R^{26} represents H or C_{1-4} alkyl;

10 R^{26a} represents C_{1-4} alkyl;

R^{27} and R^{28} independently represent H, C_{1-4} alkyl or $C(O)R^{30}$, or together represent C_{3-6} alkylene, thus forming a 4- to 7-membered ring, which ring is optionally substituted, on a carbon atom that is α to the nitrogen atom, with an =O group;

15 R^{21} , R^{22} , R^{23} , R^{24} and R^{30} independently represent, at each occurrence, H or C_{1-4} alkyl;

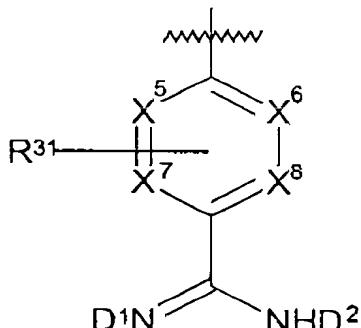
20 Y represents CH_2 , $(CH_2)_2$, $CH=CH$ (which latter group is optionally substituted by C_{1-4} alkyl), $(CH_2)_3$, $CH_2CH=CH$ or $CH=CHCH_2$ (which latter three groups are optionally substituted by C_{1-4} alkyl, methylene, =O or hydroxy);

R^7 represents H or C_{1-4} alkyl;

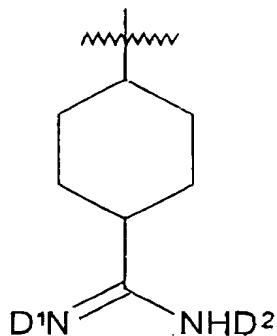
25 n represents 0, 1, 2, 3 or 4; and

B represents a structural fragment of formula IIIa or IIIc

85



IIIa



IIIc

wherein

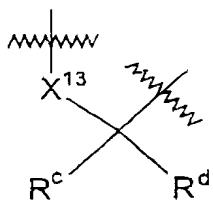
X^5 , X^6 , X^7 and X^8 independently represent CH, N or N-O;

5 R^{31} represents an optional substituent selected from halo, C_{1-4} alkyl (which group is optionally substituted by one or more halo group), $N(R^{32})R^{33}$, OR^{34} or SR^{35} ;

R^{32} and R^{33} independently represent H, C_{1-4} alkyl or $C(O)R^{36}$;

R^{34} , R^{35} and R^{36} independently represent H or C_{1-4} alkyl; and

10 one of D^1 and D^2 represents H, and the other represents OR^a , NHR^a , $C(=X^{11})X^{12}R^b$, or D^1 and D^2 together represent a structural fragment of formula IVa:-



IVa

R^a represents H or $-A^5[X^{14}]_n[C(O)]_rR^c$;

R^b represents $-A^5[X^{14}]_n[C(O)]_rR^c$;

15 A^5 represents, at each occurrence, a single bond or C_{1-12} alkylene (which alkylene group is optionally interrupted by one or more O, $S(O)_m$ and/or

N(R^f) group, and is optionally substituted by one or more of halo, OH, N(H)C(O)R^g, C(O)N(R^g)R^h, C₃₋₇-cycloalkyl (which cycloalkyl group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group and/or is optionally substituted by one or more substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, =O or =S), Het and C₆₋₁₀ aryl (which aryl and Het groups are themselves optionally substituted by one or more substituents selected from C₁₋₆ alkyl (optionally substituted by one or more halo substituent), C₁₋₆ alkoxy, halo, cyano, C(O)OR^g, C(O)N(R^g)R^h and N(R^f)R^g);
 5

10 R^c and R^d both represent H; or one of R^c and R^d represents H or C₁₋₇ alkoxy and the other represents C₁₋₇ alkyl (which alkyl group is optionally interrupted by one or more O atoms); or R^c and R^d together represent C₃₋₈ cycloalkyl, which cycloalkyl group is interrupted by one or more O, S(O)_m and/or N(R^f) group;
 15

20 R^e represents, at each occurrence, H, C₁₋₁₂ alkyl (which alkyl group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group, and/or is optionally substituted by one or more substituents selected from halo, OH, N(H)C(O)R^g and C(O)N(R^g)R^h), A⁷-C₃₋₇-cycloalkyl (which cycloalkyl group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group and/or is substituted by one or more substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, =O and =S), A⁷-C₆₋₁₀ aryl or A⁷-Het (which aryl and Het groups are optionally substituted by one or more substituents selected from C₁₋₆ alkyl (optionally substituted by one or more halo substituent), C₁₋₆ alkoxy, halo, cyano, C(O)OR^g, C(O)N(R^g)R^h and N(R^f)R^g);
 25

A⁷ represents a single bond or C₁₋₇ alkylene (which alkylene group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group, and/or are optionally substituted by one or more of halo, OH, N(H)COR^g and CON(R^g)R^h);

Het represents, at each occurrence, a five- to ten-membered heteroaryl group, which may be aromatic in character, containing one or more nitrogen, oxygen or sulphur atoms in the ring system;

n and r independently represent 0 or 1;

5 X¹¹, X¹² and X¹⁴ independently represent O or S;

X¹³ represents O or N(R^f);

R^f represents, at each occurrence, H, C₁₋₄ alkyl or C(O)R^g;

R^g and R^h independently represent, at each occurrence, H or C₁₋₄ alkyl; and

10

m represents, at each occurrence, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof;

15 provided that:

(a) A and E do not both represent O or S;

(b) E and D do not both represent O or S;

(c) when R¹ represents OR^{1d} and X₁ represents -C(O)-Z-A¹,

-Z-CH₂-S(O)_m-A²⁻ or -Z-C(O)-Z-A², then A¹ or A² (as appropriate) do not

20 represent a single bond;

(f) when X₄ represents -CH(R²³)-, R¹ does not represent OH;

(g) when A⁵ represents a single bond, then n and r both represent 0;

(f) when A⁵ represents C₁₋₁₂ alkylene, then n represents 1;

(g) when A⁵ represents -CH₂-, n is 1 and r is 0, then R^e does not represent

25 H; and

(h) the compound is not:-

(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Pro-Pab;

(R)- or (S)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Pro-Pab;

(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;

(R)- or (S)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab;
1-hydroxy-5-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;
1-hydroxy-5,7-dimethyltetralin-1-yl-C(O)-Aze-Pab x HOAc;
1-hydroxy-7-aminotetralin-1-yl-C(O)-Aze-Pab x HOAc;
5 1-hydroxytetralin-1-yl-C(O)-Aze-Pab x HOAc;
7-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;
(R)- or (S)-7-methoxy-1-methyltetralin-1-yl-C(O)-Aze-Pab;
4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab x OAc;
(S)- or (R)-1-hydroxy-4-methoxyindan-1-yl-C(O)-Aze-Pab;
10 1-hydroxy-5-methoxytetralin-1-yl-C(O)-Aze-Pab(OH);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(OH);
4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab(OH);
4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab(OMe);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab-
15 (C(O)OCH₂CCl₃);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab-
(C(O)OCH₂CH₃);
7-methoxy-1-allyltetralin-1-yl-C(O)-Aze-Pab x HOAc;
(S)- or (R)-1-hydroxy-7-chlorotetralin-1-yl-C(O)-Pro-Pab;
20 1-n-propyl-7-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;
6-chloro-4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
6,8-dichloro-4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
6-fluoro-4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
25 4-hydroxy-6-methylchroman-4-yl-C(O)-Aze-Pab x HOAc;
8-chloro-4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab x HOAc;
6-chloro-4-hydroxy-8-methylchroman-4-yl-C(O)-Aze-Pab x HOAc;
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-C(O)-i-Pr);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-C(O)-Et);

RECORDED - 10/20/03

(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-C(O)-Ch);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-allyl);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-Bzl);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab-
5 (CO-O-methallyl);
1-hydroxy-7-aminotetralin-1-yl-C(O)-Aze-Pab(OH);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-Val);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-(Me)Pab; or
9-hydroxyfluoren-9-yl-C(O)-Aze-Pab x HOAc.

10

2. A compound as claimed in Claim 1 wherein R¹ represents OH or C₁₋₄ alkyl (which latter group is optionally substituted by cyano or OH).

15

3. A compound as claimed in ~~any one of the preceding claims~~ wherein R_x represents a structural fragment of formula IIa or IIb.

20

4. A compound as claimed in ~~any one of the preceding claims~~ wherein, when R_x represents a structural fragment of formula IIa, then the dotted lines represent bonds, A and E both represent CH and D represents -CH=CH-;

25

5. A compound as claimed in ~~any one of the preceding claims~~ wherein, when R_x represents a structural fragment of formula IIa, X₁ represents optionally unsaturated C₂- or C₃-alkylene, or -Z-A³ (in which Z represents O, S(O)_m or N(R²⁵) (in which R²⁵ is as defined in Claim 1 or represents C₁₋₄ alkyl or C(O)R³⁰ and m and R³⁰ are as defined in Claim 1) and A³ represents C₁₋ or C₂-alkylene (which latter group is optionally unsaturated)).

90 claim 6

6. A compound as claimed in ~~any one of the preceding claims~~ wherein Y represents CH_2 , $(\text{CH}_2)_2$ or $(\text{CH}_2)_3$.

Clarini

7. A compound as claimed in ~~any one of the preceding claims~~ wherein B
5 represents a structural fragment of formula IIIa in which X^5 , X^6 , X^7 and
 X^8 all represent CH.

Class 1

8. A compound as claimed in any one of the preceding claims wherein,
when D^1 and D^2 together represent a structural fragment of formula IVa,
in which X^{13} is O, then one of R^c and R^d represents H or C_{1-7} alkoxy and
the other represents C_{1-7} alkyl.

Clarke

9. A compound as claimed in ~~any one of Claims 1 to 7~~, wherein, when D¹ or D² represents OR^a and R^a represents -A⁵[X¹⁴]_n[C(O)]_rR^e, and
15 (i) A⁵ is a single bond, then R^e is:-

15 (i) A^5 is a single bond, then R^e is:-

(1) A^7 -aryl, optionally substituted by one or more halo, C_{1-6} alkoxy, C_{1-6} alkyl or halo- C_{1-6} -alkyl substituents; or

(2) H or linear, branched, optionally unsaturated, and/or cyclic, C₁₋₁₂ alkyl, which cyclic alkyl group is optionally interrupted by an O atom and, optionally, a further O atom or S(O)_m group; or when

(ii) A^5 is linear or branched C_{1-12} alkylene, X^{14} is O and r is 0, then R^e is C_{1-3} alkyl or A^7 -aryl, in which A^7 is a single bond.

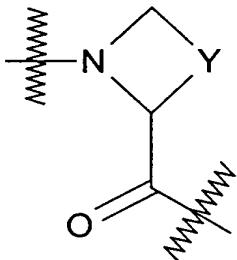
10. A compound as claimed in any one of Claims 1 to 7 or 9, wherein,
when D^1 or D^2 represents OR^a , then R^a is H or C_{1-4} alkyl.

Claim
any one of Claims

11. A compound as claimed in any one of Claims 1 to 7, wherein, when D^1 or D^2 represents $-C(=X^{11})X^{12}R^b$, in which X^{11} represents O and X^{12} represents O or S, and, in which R^b group, A^5 represents a single bond.

then R^e represents optionally unsaturated C_{1-6} alkyl, A^7 - C_{6-10} -aryl (in which A^7 represents a single bond or C_{1-2} alkylene, and which A^7 - C_{6-10} -aryl group is optionally substituted by one or more halo, C_{1-4} alkyl and/or C_{1-4} alkoxy groups), or A^7 - C_{3-7} -cycloalkyl, in which A^7 represents a single bond or linear or branched C_{1-7} alkylene, and which cycloalkyl group is optionally substituted by C_{1-3} alkyl.

12. A compound of formula I, as defined in any one of the preceding claims, wherein the fragment



10

is in the S-configuration.

13. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

14. A compound as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

15 A compound as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where inhibition of thrombin is required.

16. A compound as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the treatment of.

thrombosis.

17. A compound as defined in ~~any one of Claims 1 to 12~~, or a pharmaceutically acceptable salt thereof, for use as an anticoagulant.

5

18. The use of a compound as defined in ~~any one of Claims 1 to 12~~, or a pharmaceutically acceptable salt thereof, as active ingredient in the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is required.

10

19. The use as claimed in Claim 18, wherein the condition is thrombosis.

15

20. The use of a compound as defined in ~~any one of Claims 1 to 12~~, or a pharmaceutically acceptable salt thereof, as active ingredient in the manufacture of an anticoagulant.

20

21. A method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound as defined in ~~any one of Claims 1 to 12~~, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

22. A method as claimed in Claim 21, wherein the condition is thrombosis.

25

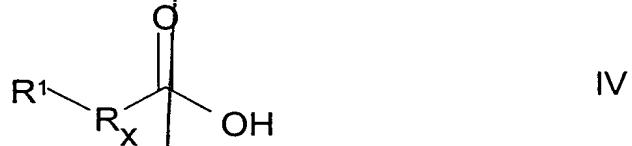
23. A method as claimed in Claim 21, wherein the condition is hypercoagulability in blood and tissues.

24. A process for the preparation of compounds of formula I which

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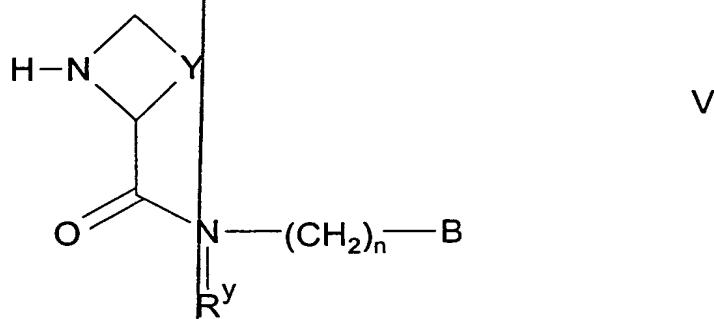
comprises:

(i) the coupling of a compound of formula IV,



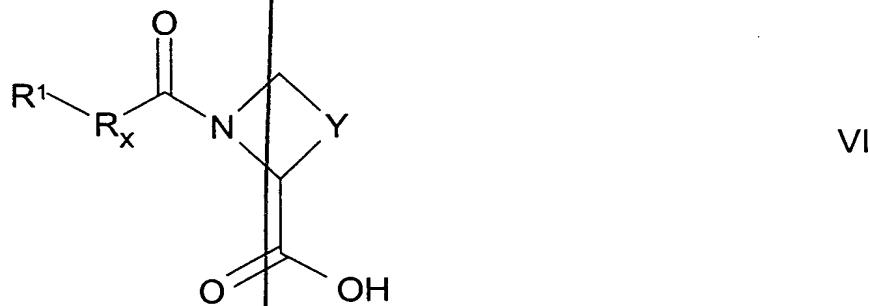
wherein R^1 and R_x are as defined in Claim 1 with a compound of formula

B2 → V,



wherein R^y , Y , n and B are as defined in Claim 1;

(ii) the coupling of a compound of formula VI,

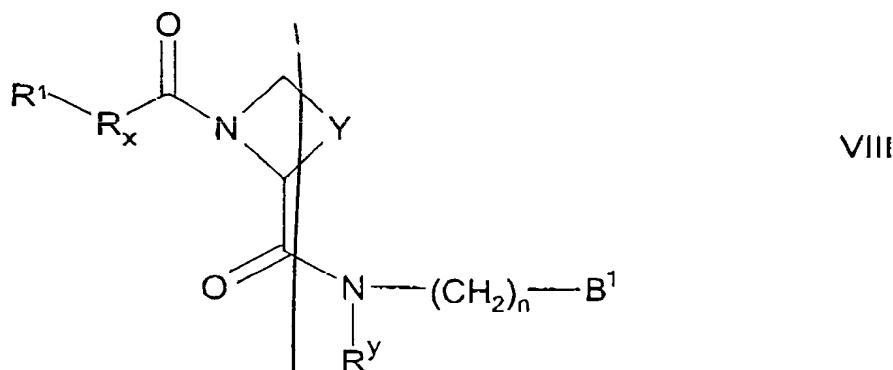


10 wherein R^1 , R_x and Y are as defined in Claim 1 with a compound of formula VII,

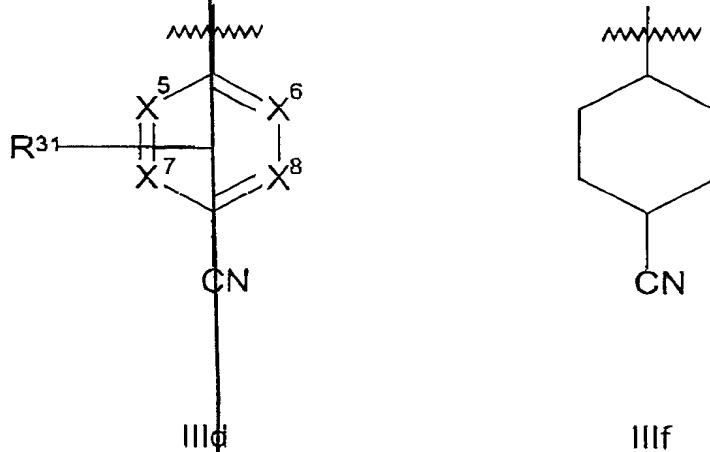


wherein R^y , n and B are as defined in Claim 1;

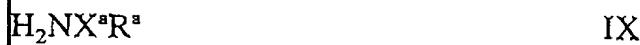
15 (iii) for compounds of formula I in which D^1 or D^2 represents OR^a or NHR^a , reaction of a compound of formula VIII,



wherein B¹ represents a structural fragment of formula IIId or IIIf



5 and $R^1, R_x, Y, R^y, n, R^{31}$ X^5, X^6, X^7 and X^8 are as defined in Claim 1
with a compound of formula IX,



wherein X^a represents O or NH and R^a is as defined in Claim 1;

(iv) for compounds of formula I in which D¹ or D² represents OR^a or NHR^a, reaction of a compound of formula I in which D¹ or D² (as appropriate) represents C(O)OR^{b1}, in which R^{b1} represents a protecting group with a compound of formula IX as defined above:

(v) for compounds of formula I in which D^1 or D^2 represents OR^a or NHR^a , R^a represents $-A^5[X^{14}]_n[C(O)]_nR^c$, in which A^5 does not represent a single bond, and n represent 1, reaction of a compound of formula I in which D^1 or D^2 (as appropriate) represents OH or NH_2 , with a compound

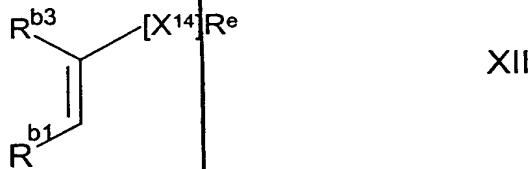
of formula X,



wherein L^1 represents a suitable leaving group, A^{5a} represents A^5 , as defined in Claim 1 except that it does not represent a single bond, and X^{14} ,

5 r and R^e are as defined in Claim 1;

(vi) for compounds of formula I in which D^1 or D^2 represents OR^a or NHR^a , R^a represents $-A^5[X^{14}]_n[C(O)]_r R^e$, in which A^5 represents C_{2-12} alkylene, which alkylene group is branched at the carbon atom that is α to the O or N atom of OR^a or NHR^a (as appropriate), and which group is optionally branched at the carbon atom that is β to that atom, n represents 1, r represents 0 and R^e is as defined in Claim 1, reaction of a compound of formula I in which D^1 or D^2 (as appropriate) represents OH or NH_2 , with a compound of formula XI,



15 or a geometrical isomer thereof, or a mixture of such geometrical isomers, in which R^{b1} and R^{b3} each represent H or an alkyl group, provided that the total number of carbon atoms provided by R^{b1} and R^{b3} does not exceed 10, and wherein X^{14} and R^e are as defined in Claim 1;

(vii) for compounds of formula I in which D^1 or D^2 represents OR^a or NHR^a , R^a represents $-A^5[X^{14}]_n[C(O)]_r R^e$, in which A^5 represents a single bond, and R^e represents A^7-C_{3-6} -cycloalkyl, in which A^7 represents a single bond, and the cycloalkyl group is interrupted by at least one O or S atom, which atom is between the carbon atom at the point of attachment to the O or NH group of OR^a or NHR^a , and a carbon atom that is α to that point of attachment, and which cycloalkyl group is optionally interrupted by one or more O or $S(O)_m$ group and/or optionally substituted by one or

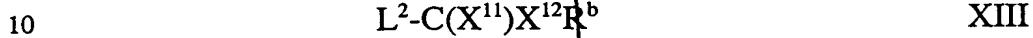
more =O group, reaction of a compound of formula I, in which D¹ or D² (as appropriate) represents OH or NH₂, with a compound of formula XII,



wherein X¹⁵ represents O or S and X¹⁶ represents C₁₋₄ alkylene (which

5 alkylene group is optionally interrupted by one or more O or S(O)_m group and/or optionally substituted by one or more =O group);

B2
(viii) for compounds of formula I in which D¹ or D² represents C(X¹¹)X¹²R^b, reaction of a compound of formula I in which D¹ and D² both represent H with a compound of formula XIII,



wherein L² represents a suitable leaving group, and X¹¹, X¹² and R^b are as defined in Claim 1;

(ix) for compounds of formula I in which D¹ and D² together represent a structural fragment of formula IVa, reaction of a corresponding compound

15 of formula I in which D¹ or D² represents OH or NHR^f (in which R^f is as defined in Claim 1), with a compound of formula XV,



wherein R^{c1} and R^{c2} both represent -OR^{c3}, in which R^{c3} represents C₁₋₃ alkyl, or together represent =O, and R^c and R^d are as defined in Claim 1;

20 (x) for compounds of formula I in which one or more of X⁵, X⁶, X⁷ and X⁸ represent N-O, oxidation of a corresponding compound of formula I in which X⁵, X⁶, X⁷ and/or X⁸ (as appropriate) represent(s) N; or

(xi) for compounds of formula I in which any one of Z, X₁, R², R⁴, A⁵, A⁷, R^c, R^d and/or R^e comprises or includes a S(O) or a S(O)₂ group,

25 oxidation of a corresponding compound of formula I (or a compound corresponding to a compound of formula I) wherein Z, X₁, R², R⁴, A⁵, A⁷, R^c, R^d and/or R^e (as appropriate) comprise(s) or include(s) a S group;

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5 (xii) for compounds of formula I in which D¹ and D² both represent H, removal of a OR^a, NHR^a or C(=X¹¹)X¹²R^b group (in which R^a, R^b, X¹¹ and X¹² are as defined in Claim 1), or removal of a structural fragment of formula IVa as defined in Claim 1, from a corresponding compound of formula I; or

(xiii) introduction and/or interconversion of a substituent on an aromatic and/or non-aromatic, carbocyclic and/or heterocyclic ring in a corresponding compound of formula I.